A comparison of the electrophysiologic effects of intravenous and oral amiodarone in the same patient

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ABSTRACT In 12 patients (nine with Wolff-Parkinson-White syndrome and three with ventricular tachycardia) the electrophysiologic effects of intravenous (5 mg/kg body weight in 1 min) and oral (total dose 9800 to 11,200 mg) amiodarone were studied with programmed stimulation of the heart. Intravenous and oral amiodarone had a similar (p < .05) effect of lengthening on the effective refractory period of the atrioventricular node. Only intravenous amiodarone prolonged (p < .05) the AH interval. Oral amiodarone was more effective than intravenous amiodarone in lengthening the anterograde effective refractory period of the accessory atrioventricular pathway. Only oral amiodarone prolonged the effective refractory period of atrium and ventricle and the HV interval, all significantly (p < .05). Intravenous amiodarone slowed (p < .05) the rate of circus-movement tachycardia in patients with Wolff-Parkinson-White syndrome, and further slowing was observed after oral amiodarone. Termination of tachycardia by intravenous amiodarone predicted prevention of reintitiation of tachycardia during oral amiodarone. These data indicate that intravenous and oral amiodarone do not have the same electrophysiologic effects. It is not clear whether cumulative effects, active metabolites, or both are responsible for these differences.


IT HAS BEEN established that amiodarone administered orally is a very powerful drug for the treatment of arrhythmias occurring at the supraventricular and ventricular level.1-8 Although its mechanism of action at the cellular level is not quite clear, the electrophysiologic effects of oral amiodarone have been well studied.2, 9-15

A major problem in using oral amiodarone is the necessity of giving the drug for several days to weeks before it can reach its maximal effect. This limits its use in patients in whom an immediate antiarhythmic effect is required. The introduction of intravenous amiodarone16 was therefore received with great interest.

In this article we report on the comparison between the electrophysiologic effects of intravenous and oral amiodarone. During programmed stimulation of the heart, we studied the effects of intravenous amiodarone in 12 patients. In the same patients the same stimulation program was repeated 5 to 6 weeks after administration of oral amiodarone.

Materials and methods

Twelve patients were studied, and their clinical data are given in table 1. After informed consent was obtained, a study of programmed stimulation was performed. Our methods of stimulation and recording and our definitions of the different electrophysiologic parameters have been reported previously.17

The following measurements were made: (1) heart rate during sinus rhythm, (2) the effective refractory period of the right atrium, (3) the effective refractory period of the right ventricle, (4) the effective refractory period of the atrioventricular (AV) node, (5) the refractory period of the accessory AV pathway (in the nine patients with Wolff-Parkinson-White syndrome), (6) the AH and HV interval, and (7) the site of origin, mechanism, and pathway of tachycardia. The effect of intravenous and oral amiodarone was studied as follows: amiodarone was given intravenously in 1 min with a dosage of 5 mg/kg body weight. Thereafter, the electrophysiologic parameters were measured immediately, 10, 20, and 30 min after administration of the drug. Each set of measurements lasted approximately 5 min.

The patient was then placed on oral amiodarone (loading dose of 600 mg/day for 1 week and maintenance dose of 200 mg/day) and was restudied 5 to 6 weeks later. At that time the total dose of amiodarone given varied individually from 9800 to 11,200 mg. During the stimulation study, similar pacing cycle lengths and premature beat intervals were used before and after the intravenous and oral administration of amiodarone.

Statistical significance of the results were analyzed with Student's t test. Apart from the cycle length during sinus rhythm,
TABLE 1
Clinical data for the 12 patients studied

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Diagnosis</th>
<th>Type of arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>46</td>
<td>WPW (left posterior)</td>
<td>CMT + AF</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>40</td>
<td>WPW (left posterior)</td>
<td>CMT</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>11</td>
<td>WPW (right lateral)</td>
<td>CMT</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>55</td>
<td>Old MI</td>
<td>VT</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>17</td>
<td>WPW (septal)</td>
<td>CMT</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>15</td>
<td>WPW (left posterior)</td>
<td>CMT + AF</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>21</td>
<td>WPW (left posterior)</td>
<td>CMT</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>20</td>
<td>WPW (left lateral)</td>
<td>CMT + AF</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>18</td>
<td>No heart disease</td>
<td>VT</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>27</td>
<td>WPW (left lateral)</td>
<td>CMT + AF</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>37</td>
<td>WPW (left lateral)</td>
<td>CMT</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>60</td>
<td>Old MI</td>
<td>VT</td>
</tr>
</tbody>
</table>

WPW = Wolff-Parkinson-White syndrome; MI = myocardial infarction; CMT = circus-movement tachycardia; AF = atrial fibrillation; VT = ventricular tachycardia.

all results are given as minimal changes from measurements obtained during predrug single-test stimulation at a basic pacing cycle length of 600 msec.

Results

With the exception of the changes during sinus rhythm, table 2 shows the maximal effect of intravenous and oral amiodarone by use of measurements made during basic pacing with a cycle length of 600 msec.

Heart rate during sinus rhythm. As shown in table 2, sinus rate behaved differently after administration of intravenous and oral amiodarone. The sinus rate did not change significantly after intravenous amiodarone but decreased (p < .05) after administration of oral amiodarone.

Refractory periods of atrium and ventricle. Table 2 shows that no change or a minimal prolongation of the effective refractory period of the right atrium and right ventricle occurred after intravenous amiodarone. Oral amiodarone, however, prolonged the effective refractory period of both the right atrium and right ventricle significantly (p < .05) by a mean of 35 and 18 msec.

Refractory periods of the AV node and the AH interval. As shown in table 2, both intravenous and oral amiodarone resulted in significant lengthening of the effective refractory period of the AV node (p < .05). There was no difference in the amount of increase between intravenous and oral amiodarone. Significant lengthening (p < .05) of the AH interval was only observed after intravenous amiodarone.

HV interval. No change in HV interval was observed after intravenous amiodarone. Oral amiodarone resulted in a mean prolongation of the HV interval by 10 msec (p < .05).

Refractory period of the anterograde accessory AV pathway. Intravenous amiodarone resulted in lengthening of the anterograde effective refractory period of the accessory AV pathway by a mean of 40 msec. Oral amiodarone resulted in further prolongation, resulting in a total increase with a mean of 90 msec. There was, therefore, a further significant increase in duration of the effective anterograde refractory period of the accessory pathway when the effect of intravenous and oral amiodarone was compared (p < .05).

Effect on tachycardia. Type, rate of tachycardia, and the effect of intravenous and oral amiodarone on cycle length of tachycardia, termination of tachycardia, and prevention of reinitiation are shown in table 3.

After intravenous administration of amiodarone, slowing in rate of tachycardia was observed in all patients with a circus-movement tachycardia in the presence of Wolff-Parkinson-White syndrome. The mean increase in RR interval was 90 msec (p < .05). This was followed in three patients by termination of tachycardia by producing a block in the AV node. In these

TABLE 2
Effect of Intravenous and Oral amiodarone on electrophysiologic parameters (all measurements in msec)

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Before amiodarone (A)</th>
<th>Intravenous amiodarone (B)</th>
<th>Oral amiodarone (C)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Mean</td>
<td>Range</td>
<td>Mean</td>
</tr>
<tr>
<td>Sinus cycle length</td>
<td>12</td>
<td>700–1090</td>
<td>799 ± 42</td>
<td>620–1000</td>
</tr>
<tr>
<td>ERP RA</td>
<td>12</td>
<td>160–320</td>
<td>232 ± 41</td>
<td>220–350</td>
</tr>
<tr>
<td>ERP RV</td>
<td>12</td>
<td>200–240</td>
<td>229 ± 7</td>
<td>210–260</td>
</tr>
<tr>
<td>ERP AVN</td>
<td>8</td>
<td>220–360</td>
<td>287 ± 31</td>
<td>260–350</td>
</tr>
<tr>
<td>ERP Ant AP</td>
<td>9</td>
<td>230–300</td>
<td>265 ± 14</td>
<td>260–350</td>
</tr>
<tr>
<td>AH interval</td>
<td>11</td>
<td>55–90</td>
<td>76 ± 10</td>
<td>65–120</td>
</tr>
<tr>
<td>HV interval</td>
<td>10</td>
<td>35–50</td>
<td>41 ± 6</td>
<td>35–50</td>
</tr>
</tbody>
</table>

ERP = effective refractory period; RA = right atrium; RV = right ventricle; AVN = atrioventricular node; Ant AP = anterograde accessory pathway.

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three patients, reinitiation of tachycardia by programmed electrical stimulation of the heart was prevented. In two of these patients, tachycardia could no longer be initiated during administration of oral amiodarone. During oral amiodarone the amount of slowing in rate of tachycardia was greater than the one observed after intravenous amiodarone (p < .05). Only lengthening of the AH interval was observed after intravenous amiodarone, while additional increases in AH interval, HV interval, and QRS width were observed after oral amiodarone (figure 1).

Of the three patients with ventricular tachycardia, slowing in rate of tachycardia was observed in two patients (30 and 50 msec, respectively). Tachycardia persisted in all three patients. In one patient, tachycardia could no longer be initiated during long-term administration of oral amiodarone.

Side effects

Intravenous amiodarone. Shortly after the injection of amiodarone, two patients complained about a warm feeling over their whole body; this was accompanied by a visible flush. It disappeared spontaneously after a few minutes. Measurements of arterial blood pressure with the cuff method revealed a short-lasting fall in systolic blood pressure up to 15 mm Hg in three other patients.

Oral amiodarone. The drug was well tolerated in all 12 patients. In four, a slight rise in SGOT value was observed. No pulmonary, thyroid, or neurologic abnormalities were found.

Discussion

After its initial introduction as an antianginal agent,\textsuperscript{16,17} amiodarone was found to have important antiarrhythmic properties.\textsuperscript{20} To compare the electrophysiologic effects of administration of intravenous and oral amiodarone, we gave the drug both ways to the same patient. Our study reveals that the electrophysiologic effects of these two forms of administering amiodarone are not the same. While the AV node was affected to the same degree, different effects were observed on the sinus cycle length, effective refractory period of the right atrium and right ventricle, the HV interval, and the anterograde refractory period of the accessory pathway.

This indicates that the study of the effect of intravenous amiodarone does not predict all electrophysiologic effects of long-term administration of oral amiodarone.

Clinically, the effects of intravenous amiodarone have been used successfully in the treatment of atrial fibrillation and atrial flutter in the postoperative and intensive-care setting.\textsuperscript{21,22} Our observations do not allow conclusions to be drawn on the applicability of intravenous amiodarone for the treatment of ventricular arrhythmias.

It is not presently clear what is responsible for the differences observed after intravenous and oral amiodarone. Are they the result of a cumulative effect after administration of amiodarone, active metabolites of amiodarone, or both? Another possibility is that a greater amount of amiodarone reached the appropriate tissues after oral administration, because after intravenous amiodarone, testing was performed during the early-distribution phase when serum and tissue level are rapidly changing.

Clinically, we have noticed that the oral administration of amiodarone in patients with atrial fibrillation results in a reduction in ventricular rate within a few hours after administration of the drug. This suggests that oral amiodarone already affects AV nodal conduction shortly after ingestion. It is therefore possible that active metabolites are responsible for most of the effects on intraventricular conduction and refactoriness of atrium and ventricle.

| TABLE 3 |
|-----------------|-----------------|-----------------|-----------------|
| Effect of intravenous and oral amiodarone on termination and prevention of reinitiation of tachycardia during programmed stimulation of the heart | Tachycardia cycle length | Tachycardia stopped by intravenous amiodarone | Reinitiation prevented (n) |
| | Before amiodarone | Intravenous amiodarone | Oral amiodarone |
| | Range | Mean | Range | Mean | Range | Mean | Intravenous | Oral |
| No. of patients | Type of tachycardia | | | | | amiodarone | amiodarone |
| 9 | CMT | 270–370 | 304 ± 28 | 270–460 | 394 ± 57 | 360–470 | 441 ± 31 | 3 | 3 | 2 |
| 3 | VT | 280–400 | ^ | 310–450 | ^ | 360–450 | ^ | 0 | 0 | 1 |

CMT = circus-movement tachycardia; VT = ventricular tachycardia.

*Since only three patients with ventricular tachycardia were studied, no mean values are given and no statistical analysis was performed for these patients.
Our study has obvious limitations. First, the number of patients is small. The necessity of waiting for several weeks before the repeat study could be performed made the investigation difficult.

Second, amiodarone was given intravenously in a dosage of 5 mg/kg body weight over 1 min. Although this has been recommended by the manufacturers, a negative inotropic effect could have partly counteracted the electrophysiologic effects of the drug.23 This might explain the absence of changes in sinus cycle length after intravenous amiodarone. Also, the method of oral dosing was less than commonly used in the United States. It would be of interest and importance to know what effect a larger loading and maintenance dose would have on the electrophysiologic parameters measured.

Third, although studies of programmed stimulation give insight into the electrophysiologic effects of amiodarone, their value in predicting clinical effectiveness of the drug is limited. Most studies have noted that

\[ \text{FIGURE 1. We recorded five extracardiac electrocardiographic leads and several intracardiac leads before administration of amiodarone (A), during intravenous amiodarone (B), and during oral amiodarone (C) to study the effects of the drug on the time intervals in a patient with Wolff-Parkinson-White syndrome suffering from circus-movement tachycardia. Note that intravenous amiodarone results in slowing of tachycardia because of an increase in AH interval. After oral amiodarone, there is additional prolongation of the HV interval, AH interval, and width of the QRS complex.} \]
while induction of tachycardia is still possible during pacing, tachycardia no longer occurs clinically.13–15,24

It is suggested that in patients with Wolff-Parkinson-White syndrome, prevention of reinitiation of circus-movement tachycardia by intravenous amiodarone predicted similar effects after oral administration. In these patients, amiodarone made the AV node the "weak link" in the tachycardia circuit. Clinically, reentrant tachycardia requires for initiation and maintenance (1) an initiating event creating unidirectional block and (2) a circuit in which the appropriate relation between conduction velocity of the circulating impulse and duration of refractoriness within the circuit must be present. Programmed stimulation of the heart can only identify beneficial effects of a drug in two ways: either by showing that administration of the drug prolongs refractoriness of cardiac tissue, thereby preventing the occurrence of a initiating event creating unidirectional block, or by demonstrating that the drug disturbs the delicate interplay between conduction velocity and refractoriness within the reentry circuit. In only a limited number of patients can one of these two beneficial mechanisms be identified after administration of amiodarone. One has to conclude that it is difficult if not impossible to predict the individual antiarrhythmic effects of amiodarone from the outcome of electrophysiologic studies. Prevention of the spontaneously occurring premature beat, which acts as the tachycardia-initiating event, might be an important mechanism for the antiarrhythmic effect of amiodarone in most patients.

References
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